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USSR WORK IN BIOCHEMISTRY INVOLVING USE OF THE ISOTOPE METHOD

[Comment: This report gives pertinent excerpts from an article by Academician V. Engel'gardt entitled "Isotopes in Biochemistry," published in Meditsinskiy Rabotnik, Vol 18, No 60, 22 July 1955.]

The application of the isotope method in biology has become widespread. Some danger is connected with any method which is applied on a scale as extensive as this. The isotope method has become fashionable and is sometimes used for the solution of problems which could be solved by the methods of classical analytical chemistry alone.

A particularly important result obtained with the use of the isotope method is the finding that the proteins of all tissues and cells are regenerated with great rapidity. The fluidity of the proteins of organs and tissues in the living organism and the incessant regeneration of their amino-acid composition is a fact of primary importance. This regeneration and renewal must be regarded as a result of uninterrupted processes of the dissociation of cell proteins and their resynthesis.

The concept of the fluidity and easy regeneration of proteins led some investigators to somewhat exaggerated ideas in regard to the facility with which this regeneration or renewal takes place. It has been incorrectly concluded that the renewal of the amino-acid composition of proteins can take place in systems in which ordinary processes of metabolism do not take place, for instance in blood plasma or blood serum. The capacity to regenerate their composition was even ascribed to individual, isolated proteins. Checking did not confirm the accuracy of these far-reaching conclusions: errors were discovered in the experimental methods that have led to these erroneous results.

One may regard it as certain that the entrance of amino-acid residues into the composition of the protein molecule does not take place as a result of penetration, but only in the process of a genuine synthesis of the proteins in question.

The isotope method is of exceptional importance for the clarification of rapidly proceeding reactions such as those taking place in photosynthesis, where the extreme rapidity of the process is combined with great complexity of the reactions which take place subsequently to the primary fundamental reaction, i.e. the reaction of the adsorption of a quantum of light.

Research by A. N. Vinogradova and R. V. Teys with the use of the isotope method made it possible to define for the first time in concrete terms the nature of the primary stage of photosynthesis and to demonstrate that this stage consists in photolysis, i.e. the photochemical scission of the molecule of water. In photosynthesis all oxygen is derived from water and not from carbon dioxide. In studying the assimilation of carbon dioxide by plants, A. L. Kursanov and his collaborators, by using the radioactive isotype of carbon as a tracer, discovered a new fact which is very important for the solution of the problem involved. They found that, in addition to assimilating the carbon dioxide of the atmosphere, plants are also capable of actively assimilating carbon dioxide from the soil. This carbon dioxide enters into the plant organism through the root system.

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A field in which the method of isotope tracers opens up particularly wide and significant prospects is the investigation of chemical processes on which the functions of the nerve tissues are based. This refers to functions taking place throughout the nervous system, beginning with peripheral nerves and ending with the central nervous system and its highest division, i.e. the cerebrum. The isotope method acquires a particular value in this field, because it enables us to investigate complex biochemical processes taking place in tissues and at the same time not interfere to any appreciable extent with normal physiological functions. It is perfectly clear to what extent this consideration is of importance when the chemical basis of the activity of the central nervous system has to be investigated, in view of the fact that this system possesses an unusually wide range of functions, a fine degree of regulation of functions, and a great sensitivity to all external influences. It is not surprising that the use of radioactive isotopes as tracers in the investigation of biochemical processes connected with the functioning of the nervous system has attracted the attention of research workers. Investigations of this type have been carried out on a particularly extensive scale in the USSR.

Work along these lines is carried out on objects of various degrees of complexity. The nerve-end formations in the heart and the excitable formations of the heart muscle connected with them were subjected to investigation by T. M. Turpayev at Kh. S. Koshtoyants' laboratory. The radioactive isotopes of elements which have a specific toxic action on the nerve transmission process (the salts of the radioactive isotopes of silver, mercury, and cadmium) were used successfully in this work. It was possible to obtain for the first time certain data in regard to the number of the molecules of poison which are necessary for putting out of commission the impulse transmission apparatus of the heart tissue.

In work carried out by N. P. Lisovskaya at our laboratory research with the use of radioactive phosphorus was carried out on sections of the cerebral cortex. The work done by Lisovskya established the relationship between the basic processes of energy metabolism and the reaction of the formation of phosphoproteins which from the chemical standpoint form the most mobile fraction of the proteins of brain tissue.

Particularly promising is the use of the isotope method in the study of chemical transformations which take place in the central nervous system in such functional states as rest and activity, excitation and depression. A great number of such investigations is being conducted at the Institute of Biochemistry, Academy of Sciences Ukrainian SSR, by A. V. Palladin and his collaborators. This work deals with lipoid compounds, of which brain tissue contains a considerable quantity, and nucleic acids, to which such an important role can be ascribed in various manifestations of the vital activity of the organism. Research is being carried out along the same lines by G. A. Vladimirov and his coworkers at Leningrad and by V. S. Shapot at Minsk. The last-named investigator obtained results which, just as the results of N. P. Lisovskaya, induce one to turn particular attention to the proteins of the brain tissues, i.e. compounds of a type which plays a leading role in the metabolism of any tissues or cells. Experiments by Shapot have demonstrated that the processes of the dissociation and synthesis of proteins in the brain cells are considerably stimulated in a state of moderate excitation, i.e. during the normal activity of the central nervous system. On the other hand, when there is exhaustion as a result of an excessively long period of excitation, there is a sharp lowering of the intensity with which proteins undergo transformations in the brain.

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The isotope method enables us to solve problems which cannot be solved by ordinary analytical methods. An illustration is the research carried out by N. V. Yel'tsina. The experiments conducted by her deal with one of the most vital and practically important problems of contemporary biology, namely the metabolism of malignant neoplasms.

There can be no doubt that the capacity of a malignant tumor to grow in an irrepressible, chaotic, and destructive manner is due in the final accounting to certain characteristics of metabolism which distinguish the malignant tumor from normal tissue. Innumerable investigators have attempted for decades to clarify these characteristics because after the specific traits of the metabolism of substances contained in tumors have been established, we will be able to influence this metabolism, i.e. exert an influence on the progress of the growth of malignant neoplasms.

This task proved to be very difficult. Substantially only one successful step has been made in research on this subject, i.e. in work by Warburg which carried out nearly 30 years ago. Since the date of his first investigations of metabolism in cancerous tumors, many attempts have been made to discover the secret of the metabolism of malignant cells. However, the work done subsequently has yielded very few clear results, notwithstanding the multiplicity of the methods and experimental approaches used. Thus, the observations made by Warburg and his conclusions remain until today our basic information on the specific characteristics of the metabolism of cancer cells.

Warburg discovered that the tissues of malignant tumors, as distinguished from normal tissues, continue to form lactic acid under aerobic conditions. Aerobic glycolysis is characteristic for cancer cells. This glycolysis was hitherto regarded as identical with the ordinary glycolytic decomposition of sugar which takes place in all tissues when respiration has been eliminated. The results of experiments with the use of glucose containing radioactive carbon require that this opinion be revised.

The most important characteristic of malignant tumors is their capacity to grow in a disordered and irrepressible manner. It is obvious that intensively proceeding processes of protein synthesis must form the basis of this growth.

In experiments carried out by N. V. Yel'tsina, attempts have been made to establish to what extent glucose is used in cancer cells for the synthesis of proteins.

The fact that cancer cells use glucose for synthesizing proteins was established very definitely. If cancer cells are kept during 2-3 hours in the presence of glucose labeled with radioactive carbon, and the proteins are then isolated from these cells, considerable radioactivity is detected in the proteins thus isolated. However, the radioactivity is apparent only when the cells have been kept together with the sugar under aerobic conditions and when aerobic glycolysis has taken place in them. Glycolysis taking place under anaerobic conditions or whenever there is respiration but no glycolysis (i.e. after poisons which inhibit glycolysis have been added), does not result in the synthesis of proteins from the decomposing glucose. It follows that aerobic glycolysis is qualitatively different from the ordinary glycolysis which takes place under anaerobic conditions. Without using radioactive isotopes and applying the method of radioactive tracers, it would not have been possible by relying solely on the methods of biochemical analysis to establish any difference between anaerobic, metabolically ineffective glycolysis, and aerobic glycolysis which has a high metabolic effectiveness. The final product, i.e. lactic acid, is the same in both cases.

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The isotope method enables us to understand more perfectly the specific characteristics of cancer cells and those characteristic aspects of its metabolism which are particularly important, because they pertain to the most important process taking place in the cell, namely the synthesis of its proteins.

It can be seen from the examples mentioned above, that certain fundamental scientific problems are seen in an entirely new light as a result of research using radioactive isotopes, i.e. products of nuclear reactions.

By acquiring a knowledge of the chemical processes on which the activity of the nervous system is based, we will elucidate the nature of the highest and most complex form of matter.

Acquisition of an understanding of the nature of photosynthesis will enable us to control a process on which the existence of all living matter on earth depends. Knowledge of the photosynthesis will also make it possible to reproduce in simple nonliving systems the processes of direct photochemical utilization of the radiant energy of the sun. Every step along this path will lead to increased food supplies and reduction of the threat of starvation and need.

The conquest of cancer as a result of research done with the aid of radioactive isotopes will eliminate one of the most dangerous human diseases. The significance of these problems goes much beyond the limits of biology. Only the first steps have been made in research with the aid of radioactive isotopes. However, one may see that work along this line is developing with an accelerating speed similar to that of chain reactions which result in the formation of radioactive isotopes. Scientists must derive a great amount of satisfaction from the knowledge that these developments based on work in the field of atomic energy will not result in an extermination of human life, but in scientific progress that will be of benefit to humanity.

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